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LIVER METASTASES FROM THYROID PRIMARY, DIFFERENTIATING FROM THYROID VARIANT OF CHOLANGIOCARCINOMA BY IMMUNOHISTOCHEMISTRY- A RARE CASE REPORT IN A TERTIARY CARE CENTER

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INTRODUCTION

Differentiated thyroid carcinoma, enclosing follicular and papillary carcinomas, has a good prognosis and long-term survival rates. Certainly, the 10-year survival rate is 80–95%. The incidence of distant metastases at the time of initial presentation of differentiated thyroid carcinoma (DTC) is 4%. Distant metastases occur primarily in the lungs (78%), followed by intrathoracic lymph nodes (58%), neck lymph nodes (51%), pleura (29%), adrenal glands (24%), *liver (20%)*, brain (18%), heart (18%), and retroperitoneal lymph nodes (18%). The presence of distant metastases is the most significant prognostic factor and is associated with poor outcomes. Only 50% of patients survive 10 years after a diagnosis of the metastatic DTC.[1–3]

Liver metastases from differentiated thyroid carcinoma (LMDTC) are rare, with a reported frequency of 0.5%. They tend to occur during the terminal phase of the disease are a grave event. Because of this rarity, there is little information available on the diagnosis and management of LMDTC.

Here we discuss about a rare case presentation with features correlating to Liver metastases from differentiated thyroid carcinoma.

CASE REPORT

A 80 year old female presented with history of cough and breathlessness for 2weeks. History of abdominal distention and loss of appetite since a year. On examination of abdomen- Hepatomegaly was observed. Clinically patient was diagnosed and treated for Cardiogenic pulmonary edema.

On HRCT thorax showed cardiomegaly and right sided pleural effusion more than left side.
On CT Abdomen contrast showed a large heterogenous enhancing mass lesion with lobular surface replacing the left lobe of liver with size, measuring 13×8.8×8.4cm. And the probable differentials were atypical multifocal hepatocellular carcinoma of liver, or angiosarcoma of liver.

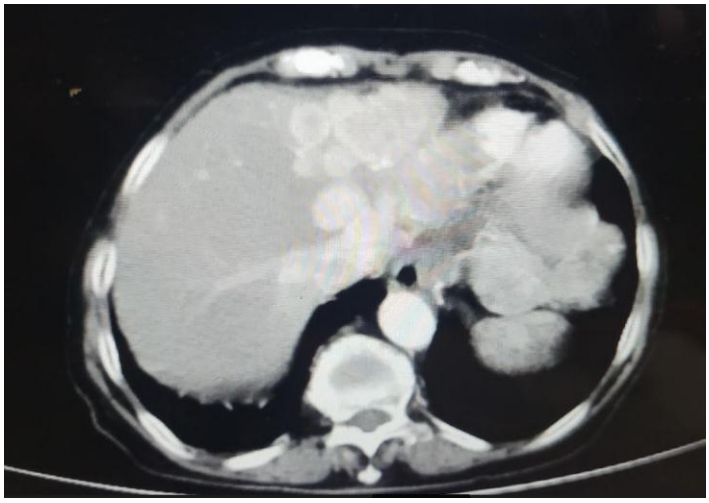


Fig.1.8 CT Abdomen showed large heterogenous enhancing mass with lobular surface replacing the left lobe of liver.

On lab investigation SGPT was 93 IU/L (**raised**) and Alkaline phosphatase 116 IU/L and Alfa fetoprotein 3.51ng/ml were within normal limits.

In view of hepatocellular carcinoma a core needle biopsy from liver was sent for histopathological examination.

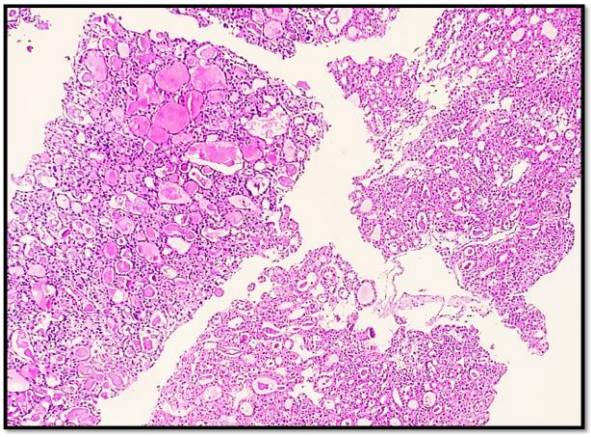
Biopsy from liver-Grossly, received 3 linear grey white soft tissue fragments each measuring 0.6×0.1cm all embedded in one block.

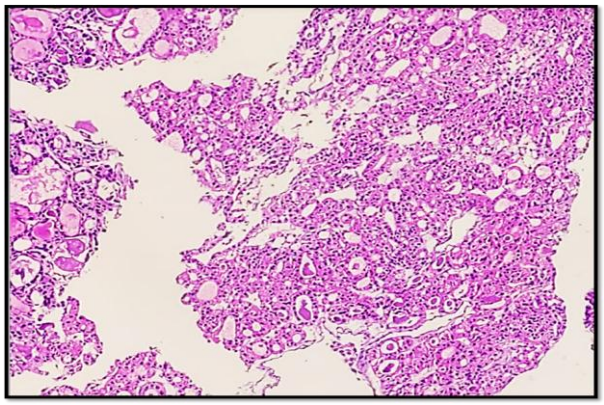
Microscopically, revealed multiple sections showing cords and trabecular pattern of *hepatocytes* with adjacent malignant neoplasm **(Fig1.1)** composed of **colloid filled follicles** lined by cuboidal epithelium with mild to moderate anisonucleosis, moderate eosinophilic

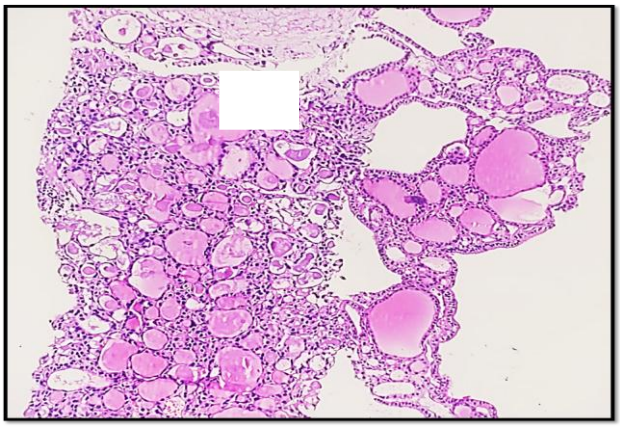
cytoplasm. (**Fig 1.3**) These follicles are separated by thick fibrous septae. No mitotic activity or necrosis. Focal areas of hemorrhage with fibrin material seen.

Impression was given as liver biopsy showing metastatic carcinomatous deposit, probably from thyroid.

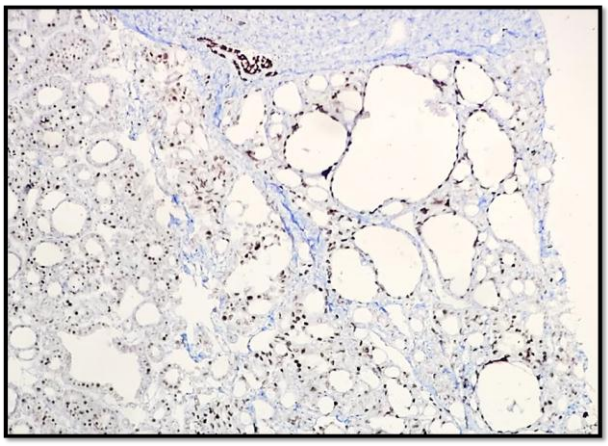
And suggested immunohistochemistry and **PET-SCAN** for confirmation.

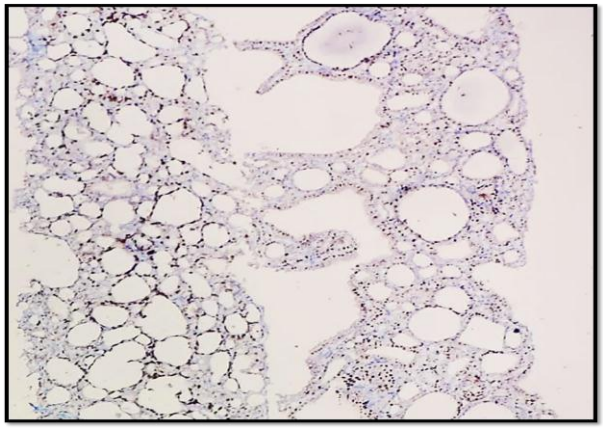






In view to know whether the primary tumor is from thyroid and to rule out lung primary we did TTF1, which showed **95 %** of tumor cells (thyroid) showing strong nuclear positivity.



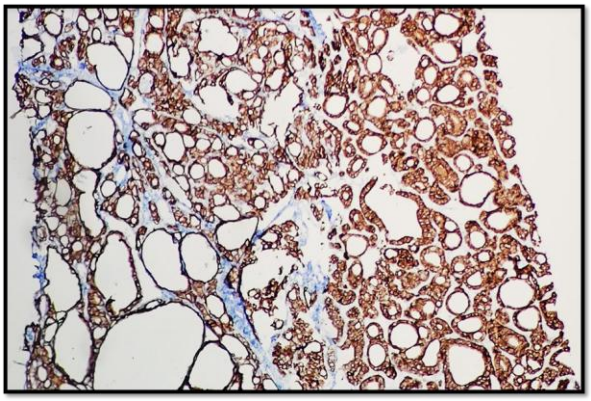


In view to know unknown primary tumor, and also to differentiate cholangiocarcinoma we did CK 7 and CK 19.

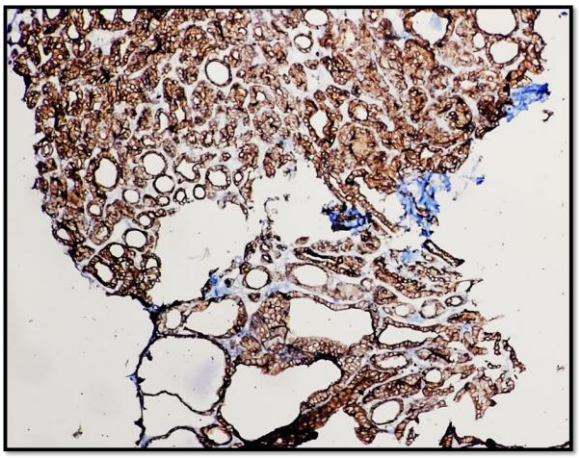
CK 7 showed 100 % of tumor cells strong cytoplasmic positivity.

CK19 showed 100% of tumor cells strong cytoplasmic positivity.

CK7



CK19



From IHC panel, we observed TTF1 positive in thyroid follicular cells, confirms thyroid tissue. In CK19 postivity indicates, tumor might me cholangiocacinoma and rules out hepatocellular carcinoma (CK19 -ve). CK 7+ve and CK 19 +ve indicates in favour of intrahepatic cholangiocarcinoma. Also CK7 +ve in thyroid carcinoma. But cholangiocarcinoma donot show TTF1 positivity.

Hence, with TTF1 positivity and CK 7 positivity in IHC and histopathologically showing thyroid follicles with colloid secretions, we conclude in favour of thyroid primary tumor.

On PETCT scan showed metabolically active calcified heterogeneously enhancing nodule in the lower pole of right lobe of the thyroid- *Likely primary malignancy*. Multiple *metastatic,* metabolically active hyperenhancing lesions involving the entire enlarged **left lobe of the liver** with few small enhancing lesions in the **segment VIII and V.** *Metastatic*, metabolically active **lytic lesion** in the body of **C5 vertebra** with minimal right paravertebral soft tissue component encasing the vertebral artery.

DISCUSSION

Liver metastases from differentiated thyroid carcinoma (LMDTC) are rare(0.5%) and usually occur in disseminated metastatic disease.[7] The diagnosis of liver metastases was established on the association between elevated thyroglobulin and imaging studies (PET, MRI, CT scan, scintigraphy) showing a tumor lesion appearance. Metastases to the liver appear to be an *advanced* manifestation of metastatic thyroid cancer in association with other metastatic sites. Because of a dedifferentiation process, most cases of LMDTC do not uptake iodine, therefore limiting the effectiveness of radioiodine therapy. Targeted chemotherapy show promising

results in patients with LMDTC; however; larger studies are needed to confirm this preliminary data.[4]

The most common sites of metastases were the lungs (78%), intrathoracic lymph nodes (58%), neck lymph nodes (51%), pleura (29%), adrenal glands (24%), *liver (20%),* brain (18%), heart (18%), and retroperitoneal lymph nodes (18%).

Cholangiocarcinoma is the third most common malignant neoplasm of liver. Many morphological patterns of cholangiocarcinoma have been described including tubular, mucinous adenosquamous, clear cells, sarcomatoid, lymphoepithelioma-like, etc.

However, the most unusual variant is the 'thyroid-like' variant of cholangiocarcinoma.[5] Microscopically, showed a prominent follicular architecture, resembling thyroid neoplasm with a combination of macro- and micro-follicles with colloid-like material. Eosinophilic *colloid-like secretions* in the neoplastic follicles. Microfollicular architecture with prominence of *"Orphan Annie eye"* nuclei. The immunohistochemical profile showed negative for thyroid-related markers -TTF-1 and thyroglobulin; positive for cholangiocarcinoma markers- CK7, and CK19.[5]

It is essential to differentiate from follicular variant of papillary thyroid carcinoma**.** Tumor nodule separated from surrounding thyroid follicles by a thin capsule. Macrofollicular pattern of the thyroid tumor with eosinophilic secretions in the lumen, similar to areas seen in the cholangiocarcinoma. Subtle nuclear grooving and focal clearing in the thyroid tumor, characteristic of follicular variant of papillary thyroid carcinoma.

On immunohistochemistry, tumor showed strong positivity for CK7 and focal for CK19 (not shown here). Intrahepatic cholangiocarcinoma is negative for thyroid specific markers, i.e. TTF-1 and Thyroglobulin. Immunohistochemical profile of thyroid carcinoma Thyroid tumor is encapsulated and has a microfollicular pattern. The tumor is diffusely positive for thyroid related markers, namely PAX8, TTF-1 and thyroglobulin.

TTF-1 and PAX-8 are tissue-specific transcription factors expressed in the thyroid follicular cells, contributing to the maintenance of the differentiated phenotype.[6] TTF-1 mRNA is always well detectable in *papillary* carcinomas and, in contrast, always absent in anaplastic carcinomas. Thus, TTF-1 gene expression could be a molecular marker in order to distinguish these two types of thyroid neoplasms.

CK immunoprofile of CC varies according to the location of the tumor in the biliary tract, peripheral CC being more often CK7+/CK20-, and nonperipheral ones CK7+/CK20+; colorectal carcinoma metastasis(CRM) were all positive for CK20 with a high intensity, and mostly negative for CK7;and the decision is based on CK20 and CK7 positivity allows the distinction of CRM and CC, even for the nonperipheral type.[7]

CK19-positive HCC is also known as biphenotypic HCC; that is, having the pathological features of both HCC and cholangiocarcinoma (CC) It is well acknowledged as a biliary/progenitor cell marker and a marker of tumor stem cell[8]Along with the development of fetal liver, these bipotential progenitor cells differentiate either into *hepatocytes* or *biliary epithelial cells.*[9]

However, the expression of CK19 is *vanished in mature liver hepatocytes* while it is constantly present in biliary epithelial cells.[9] Therefore, this explained the reason why CK19 became a significant marker of biliary epithelial cells in pathological diagnosis.

If all HCC cells were originated from hepatocytes, these HCCs would only express hepatocyte-related markers (**HEP-PAR, CK8 and CK18**).

Other markers-HEP-PAR, CK8 and CK18 –HCC markers; PAX8-thyroid neoplasm.

CONCLUSION

Rare distant sites of metastases from DTC include lungs, eyes, adrenal glands, kidneys, esophagus, pancreas and liver. Multiple liver metastases from PTC are exceedingly rare, which to differentiated from thyroid variant of cholangiocarcinoma by using immunohistochemistry is challenging.

As our patient, presented with multiple liver metastasis from PTC and metastases to vertebrae in elderly age, should be considered for palliative care with chemotherapy rather than surgical resection.

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